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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,277	12/04/2003	Gary J. Rosenthal	42830-10010	7142
25231 7590 01/05/2007 MARSH, FISCHMANN & BREYFOGLE LLP 3151 SOUTH VAUGHN WAY SUITE 411 AURORA, CO 80014			EXAMINER ROBERTS, LEZAH	
			ART UNIT	PAPER NUMBER
			1614	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/05/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/728,277

Applicant(s)

ROSENTHAL ET AL.

Examiner

Lezah W. Roberts

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 September 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 15, 17, 19, 20, 22, 24, 25, 31, 35, 38, 133-137 and 142-148 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 15, 17, 19-20, 22, 24-25, 31, 35, 38, 133-137 and 142-148 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f):
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date A-B.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

This office action is in response to the amendment filed September 29, 2006. All previous rejections have been withdrawn unless stated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action mailed March 23, 2006.

### ***Response to Declaration Under 37 CFR 1.132***

The Declaration of Janice M. Troha under 37 CFR 1.132 filed September 29, 2006 is insufficient to overcome the rejection of the instant claims based upon 35 USC 102 and 103 as set forth in the last Office action because: the Declaration shows methods of using the compositions. The claims are directed to a composition, however not a method of use. The intended use of a composition carries no weight in determining patentability because the compositions suggested by the references are substantially the same as the compositions of the instant claims.

### ***Claims***

#### **Claim Rejections - 35 USC § 103 (Previous Rejection)**

Claims 15, 22-23 and 136-141 were rejected under 35 U.S.C. 103(a) as being unpatentable over Krezanoski (US 4,188,373) in view of Boggs (US 5,358,705). The rejection is maintained in regards to claims 15, 22, 136-137 and 140.

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Applicant argues Krezanoski does not disclose N-acetylcysteine (NAC), for any purpose. Applicant further argues based on the Troha Declaration, the disclosure of Boggs et al. would not lead to an expectation that NAC would be efficacious for treatment of mucositis occurring as a side effect of cancer therapy, the pathogenesis of which does not appear to be due to the presence of bacteria.

In response to applicant's argument that Krezanoski does not disclose NAC for any purpose and the disclosure of Boggs et al. would not lead to an expectation that NAC would be efficacious for treatment of mucositis occurring as a side effect of cancer therapy, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

**Claim Rejections - 35 USC § 103 – Obviousness (New Rejection)**

Claims 1, 15, 19, 31, 35, 38, 133-137, 142-143 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi et al. (US 6,503,955).

Dobrozsi et al. disclose pourable liquid vehicles comprising an aqueous or nonaqueous polymer solution. The vehicles comprise a polyoxyalkylene block copolymer, water and glycols. The copolymer comprises polyoxypropylene and polyoxyethylene and makes up 25% to 77% by weight of the vehicle. Water makes up

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5% to 45% of the composition (col. 7, lines 5-25). The glycols used, such as polyethylene glycol, which encompasses claim 31, make up 0 to 70% (col. 6, lines 50-53). Pluronic F-127 is a preferable block copolymer used in the compositions. The pourable liquid vehicle of the disclosed invention were formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture (col. 4, lines 33-48). The viscosities of the formulated vehicles were measured at room temperature and 37°C, the temperature inside the human body. It was disclosed the viscosity of the compositions increased at the higher temperature, therefore encompassing claim 1. The disclosed liquid compositions have a viscosity of less than about 7 pascal seconds, preferably less than about 2 pascal seconds, more preferably less than about 1 pascal seconds (col. 5, lines 12-17), which encompasses no larger than 60cP of the instant claims. The desired value of a composition's triggered viscosity ratio is least about 1.3, preferably at least about 2, more preferably at least about 5, and most preferably at least about 10. The triggered viscosity is defined as the viscosity of the gel divided by the viscosity of the liquid. Using this calculation the gel viscosity is greater than 80cP, which encompasses the instant claims. The pourable liquid vehicles have a number of utilities including delivery of therapeutic agents. These include agents selected from the group consisting of expectorants/mucolytics, antioxidants and mixtures thereof (col. 7, lines 28-51). Expectorants/mucolytics include N-acetylcysteine. The active agents are added to the vehicles ranging up to 5% weight of the total composition according to the disclosed examples, which encompasses claim

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15. The reference discloses several different dosage forms including gels, rinses, sprays and liquid filled capsules for intra-oral administration. Flavors and preservatives are also used in the disclosed compositions (see examples), as recited in claims 35 and 38.

The reference differs from the instant claims insofar as it does not disclose specifically using N-acetylcysteine in a composition comprising poloxamers 407. The reference is not anticipatory insofar as one must "pick and choose" from different lists of active agents and poloxamers. That being said, it would have been obvious in a self-evident manner to have selected N-acetylcysteine from one list and poloxamers 407 from another, motivated by the unambiguous disclosure of each individually, and consistent with the basic principle of patent prosecution that a reference should be considered as expansively as is reasonable in determining the full scope of the contents within its four corners.

2) Claims 17, 20, 24-25 and 137, 140, 144-145 and 147-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi et al. (US 6,503,955) in view of Stratton et al. (US 5,861,174).

The primary reference is discussed in subsection 1, above. The reference differs from the instant claims insofar as it does not disclose the compositions comprise 0.1 to 20% of the preferred block copolymer, the compositions comprise about 10% or N-acetylcysteine and the composition were made when the liquid carrier was 5°C.

Stratton et al. disclose pharmaceutical compositions for the delivery of pharmacologically active proteins. The polypeptides make up 0.5% or greater of the disclosed compositions (col. 3, lines 38-45). In one embodiment of the invention, the polypeptide comprises 0.5 to 50% by weight of the compositions (col. 6, lines 46-50). The polymers of disclosed invention provide a sustained release delivery system for active agents or drugs (col. 1, lines 51-53). The delivery vehicle comprises block copolymers, polyoxyethylene-polyoxypropylene, namely Pluronic polyols, or poloxamers. Poloxamers have the ability to gel as a function of temperature and polymer concentration. Poloxamers having molecular weights below 10,000, do not form gels at any concentration, therefore Pluronic F-127 and Poloxamer 407 are the polymers of choice for the disclosed invention (col. 2, lines 18-60). These polymers have the characteristics of being liquid at temperatures below room temperature but will form a gel as they are warmed (col. 4, lines 38-41). The aqueous polymer solutions may be formed in two ways, by a cold process or by a hot process. The cold process involves dissolving the polymer at a temperature from about 5°C to 10°C (col. 5, lines 20-34). When adding the polypeptide, it is preferred to add the agent at a temperature of about 0°C to 10°C. These conditions encompass claims 24-25. Raising the sample temperature above the gel point of the poloxamer results in an even distribution of protein particles throughout the polymer gel (col. 6, lines 1-7). The copolymer will not form a gel at a concentration outside the range of about 20% to 30% by weight (which overlaps the concentration of the instant claims), but it was discovered other compounds could be added to the compositions in order for the copolymer to form a gel

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at concentrations lower than 20% by weight, which encompasses claim 137 as well as claim 20.

The reference differs from the instant claims insofar as it does not disclose compositions comprising glutathione or its precursors and the viscosities of the compositions before and after the temperature change.

It would have been obvious to adjust the amount of poloxamer in the compositions of the primary reference motivated by the desire to obtain the desired characteristics of the composition, such as the removal of the reverse-thermal gelation property as recited in claim 20, as disclosed by the secondary reference.

It would also have been obvious to one of ordinary skill in the art to have used the delivery system comprising 20 to 30 percent poloxamer and theory to deliver the active agents of the primary reference motivated by the desire to provide a sustained release composition that exist in a liquid form and gels when introduced into the body wherein the therapeutic composition is released over a period of time, as disclosed by the secondary reference.

Normally, changes in result effective variables are not patentable where the difference involved is one of degree, not of kind; experimentation to find workable conditions generally involves the application of no more than routine skill in the art. In re Aller 105 USPQ 233, 235 (CCPA 1955). It would also have been obvious to one of ordinary skill in the art to have adjusted the amount of N-acetylcysteine in the compositions of the primary reference motivated by the desire to deliver an effective amount of active agent to obtain optimal results, as supported by cited precedent.

3) Claims 1, 15, 20, 22, 24-25, 35, 38, 137, 140 and 142-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boggs (US 5,358,705) in view of Stratton et al. (US 5,861,174).

Boggs et al. disclose oral compositions for preventing conditions of the oral cavity. The active ingredients in the compositions include N-acetylcysteine complexes, which make up 0.05 to 10% of the compositions as recited in the instant claims. These concentrations are considered "safe and effective", which is defined as an amount of compound or composition sufficient to induce a significant positive modification in the condition being treated, but low enough to avoid serious side effects (col. 4, lines 11-32). The compositions also include surfactants such as Pluronic F-127 and make up 0 to 10% of the compositions. The reference differs from the instant claims insofar as it does not specifically disclose the compositions exhibit thermal-reversible behavior.

The secondary reference is discussed above and disclosed the thermal properties of polyoxyethylene and polyoxypropylene copolymers. It is used as a general teaching to show the surfactants used in the compositions of the primary reference are thermal responsive polymers and do not display thermal responsive gelation at the disclosed concentrations. The reference differs from the instant claims insofar as it does not disclose comprising N-acetylcysteine in the compositions.

It would have been obvious to one of ordinary skill in the art to have used the amounts of poloxamer used in the compositions of the primary reference motivated by the desire to inhibit gel formation but still has an increased viscosity when introduced

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into the body to prolong the release of the active agent, as disclosed by the secondary reference.

Claims 1, 15, 17, 19-20, 22, 24-25, 31, 35, 38, 133-137 and 142-148 are rejected.

No claims allowed.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

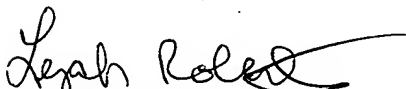
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Lezah Roberts  
Patent Examiner  
Art Unit 1614

  
Frederick Krass  
Primary Examiner  
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